ISN Forefronts Symposium 2010 in Sylt, Germany: 'Induction and Resolution of Renal Inflammation'

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The International Society of Nephrology (ISN) Forefronts Symposium 'Induction and Resolution of Renal Inflammation' took place in May 2010 on the Island of Sylt, Germany. The program included basic and clinical aspects of inflammation with a special focus on human and experimental glomerulonephritis. Distinguished scientists from different fields of inflammation research reported their recent discoveries and discussed emerging topics including the role of resolution for inflammatory processes; the 'new and old' cellular players of innate immunity and their mediators; the fundamental role of T-cell subtypes and chemokines; new aspects of B cell-mediated immune responses; and finally the potential implication of results from basic science for human inflammatory renal disease.

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Inflammation is the complex biological response of the immune system to a great variety of harmful stimuli. This process of tightly controlled cellular and biochemical events has evolved to eliminate invading pathogens, remove damaged or abnormal cells, and preserve tissue integrity. Impaired self-tolerance and uncontrolled activation of the immune system can result in deleterious inflammatory responses, ultimately leading to autoimmune disease.

Inflammatory renal disease develops when uncontrolled immune activation directly targets kidney antigens, as in anti-glomerular basement membrane disease and membranous nephropathy, or when systemic autoimmunity involves kidney structures, as in small-vessel vasculitis or systemic lupus. Production of proinflammatory cytokines and chemokines by resident kidney cells and infiltrating leukocytes initiate and perpetuate the inflammatory process, resulting in tissue damage and loss of renal function.

In the past decades, extensive studies on the molecular signaling pathways that initiate the inflammatory cascade and recruit immune cells to the site of inflammation have identified critical mediators in this process. Contrariwise, the mechanisms that downregulate inflammation and switch the immune response toward resolution remain only incompletely understood. Recent studies indicate that the resolution of inflammation is an active process requiring activation of endogenous signaling pathways that counter-regulate the inflammatory response. Understanding the molecular requirements for resolution may facilitate the development of drugs that can be used to resolve unwanted inflammation in acute (and chronic) inflammatory conditions in humans.

This report describes the highlights from the International Society of Nephrology (ISN) 2010 Forefronts Symposium 'Induction and Resolution of Renal Inflammation,' which took place from 06 to 09 May 2010 in Sylt (Germany).

RESOLUTION OF INFLAMMATION

Dr Derek W. Gilroy (University of London, UK) gave an overview of this emerging field in the keynote lecture 'Resolution of inflammation: state of the art, definition and terms.' He provided details of how the study of resolution in acute and chronic inflammation might help in developing

novel anti-inflammatory therapeutics, and defined key terms and components of interest in the resolution process.[1] Dr. Gilroy discussed his recent work on cyclooxygenase and lipoxygenase-derived lipid mediators (cyclopentenone prostaglandins, prostaglandin D_2, lipoxins, and aspirin-triggered epi-lipoxins) that limit the continuity of inflammatory responses. He furthermore addressed the current understanding of cellular players in this setting and introduced some new soluble mediators (resolvins) and their receptors as novel, potentially pro-resolving agents.[2]

Dr Adriano G. Rossi (University of Edinburgh, UK) addressed the importance of apoptosis for clearance of potentially injurious inflammatory cells, such as neutrophils, and highlighted the role of apoptosis for efficient resolution of inflammation. Subsequently, he discussed novel strategies for termination of deleterious inflammatory responses with a special focus on translation of these strategies into pro-resolution therapies.[3]

Dr Jeremy Hughes (University of Edinburgh, UK) provided an overview of the function of inflammatory cells in renal repair and resolution with a special focus on neutrophils and monocytes/macrophages.[4] More specifically, he discussed the basic mechanisms involved in the potential partnership of neutrophils and macrophages during time course of the inflammatory response. Finally, he highlighted that apoptotic neutrophils are capable of reducing tissue damage by releasing soluble factors (for example, α-defensins) that can inactivate lipopolysaccharide-stimulated macrophages.[5]

Dr David C. Harris (University of Sydney, Australia) discussed the pro- and anti-inflammatory roles of macrophages in renal inflammation. Macrophage infiltration is a morphological hallmark of human and experimental chronic kidney disease. The degree of macrophage infiltration correlates with the severity of injury, suggesting a causal link. However, macrophages are a heterogeneous population of cells, some of which are proinflammatory and pathogenic (M1) and others that are anti-inflammatory and protective (M2a-c types).[6] M2-programmed macrophages prepared *ex vivo* and transferred into recipient mice with inflammatory renal disease have been shown to ameliorate tissue injury by modulating effector functions of pathogenic macrophages and T cells in the kidney.[7] Before these phenotypically diverse cells could be used as a therapeutic tool for human kidney disease, the understanding of macrophage biology has to be improved by further studies.

INNATE IMMUNE RESPONSE: NEW AND OLD CELLULAR PLAYERS AND MEDIATORS

Two sessions focused on aspects of the innate immune response. These included the classical players of innate immunity (neutrophils, complement factors, and the Toll-like receptor (TLR) family), as well as innate cell types that have just recently attracted attention in experimental nephrology, namely basophilic granulocytes, mast cells, natural killer T cells, and dendritic cells (DCs). The speakers provided mechanistic insight into recently discovered functions of these cells in basic immunology and experimental models of nephritis.

In his talk, 'New insight in the role of basophils in immune regulation,' *Dr Matthias Mack* (University of Regensburg, Germany) highlighted recent technical advances that permit detection and analysis of these rare cells in patients and in murine disease models. Taking advantage of these techniques, his group recently demonstrated that basophils are important contributors to humoral memory immune responses. The basophil-dependent effects on B cells required interleukins 6 and 4 (IL-6 and IL-4), and increased the capacity of $CD4^+$ T cells to provide B-cell help.[8] These findings shed new light on the pathogenesis of antibody-mediated diseases and may have an impact on vaccine development.

Dr Stephen Holdsworth (Monash University, Melbourne, Australia) provided an overview about the role of mast cells in autoimmune disease and glomerulonephritis. Mast cells are involved in allergy and anaphylaxis, as well as in the defense against pathogens. Recently, mast cells have been suggested to participate also in human renal disease;[9] however, their exact functional role remains to be defined. In mast cell-deficient W^{sh} mice, autoimmune anti-myeloperoxidase (MPO)-mediated glomerulonephritis was significantly enhanced, as was autoimmunity to MPO compared with wild-type mice. These data suggest that mast cells may maintain peripheral tolerance to the vasculitis-associated autoantigen MPO.

Dr Christian Kurts (University of Bonn, Germany) introduced a new concept of DC-mediated cytotoxic T lymphocyte activation. Specialized DCs induce cytotoxic T lymphocyte responses against extracellular antigens, such as viruses, bacteria, or vaccines, using a mechanism termed cross-priming.[10] DCs require cognate 'licensing' for cross-priming that denotes stimulatory signals from T helper (Th) cells that switch the DCs into a functional state capable of immunogenic T-cell priming. This is called 'classical cross-priming.' Dr Kurts demonstrated an alternative mechanism of cognate licensing by the so-called natural killer T cells that recognize lipid instead of peptide antigens.[11] These findings have relevance for basic immunology, showing that DCs can be licensed for cross-priming by natural killer T or Th cells, depending on the type of antigen they encounter. Natural killer T and Th cells use at least two independent chemokine pathways (chemokine (C-C motif) receptor 4 and 5 (CCR4 and CCR5)) to attract naive cytotoxic T lymphocytes that acted synergistically and may be exploited to improve vaccinations.[11]

Dr Stephan Segerer (University of Zürich, Switzerland) provided an overview of the role of DCs in human glomerulonephritis. Descriptions of cells with dendritic morphology in rodent kidneys date back to the early 1970s. During the 1980s and 1990s, HLA-DR-positive DCs were found to be localized in normal renal tissue and in the interstitium from patients with glomerulonephritis.[12,13] Numerous recent experimental studies revealed their involvement in

models of renal injury, for example, their ability to capture and present glomerular antigens to kidney-infiltrating Th cells.[14] Th cells responded with cytokine and chemokine production that attracted immune effector cells that drive nephritis progression. The functional role of different DC subtypes in human kidneys has still to be fully elucidated.

Dr Eicke Latz (University of Bonn, Germany) introduced the recently described innate immune receptor family of Nod-like receptors (NLRs). The NLR member NLRP3 and the adapter protein ASC form a multimolecular complex termed the NLRP3 inflammasome.[15] Inflammasomes control the activity of caspase-1 that cleaves and activates the proform of inflammatory cytokines IL-1β and IL-18. He demonstrated that crystal uptake by cells that leads to lysosomal damage and rupture can activate the NLRP3 inflammasome in a process that requires phagocytosis. These results indicate that the NLRP3 inflammasome can sense lysosomal damage as an endogenous danger signal, representing a novel strategy of immune cells to recognize different classes of harmful stimuli by a common mechanism.[16]

Dr Hans-Joachim Anders (University of Munich, Germany) discussed the role of TLRs in renal inflammation.[17] Signs of renal inflammation are observed in many of the so-called noninflammatory kidney diseases, for example diabetic nephropathy. TLR research might provide an explanation for this finding, as TLR-mediated activation of the innate immune system can be induced by both pathogen-derived and nonpathogen-derived immunostimulatory molecules. Thus, metabolic, hemodynamic, toxic, or autoimmune forms of tissue damage can all trigger an innate inflammatory response. As immune activation is unable to eliminate the underlying drivers of nonpathogen-associated diseases, it merely leads to unwanted aggravation of renal damage.[18] The fact that genetic variants in danger-signaling genes of the innate immune system can affect the individual risk for insufficient pathogen control or exaggerated nonpathogen-related renal tissue pathology underlines the importance of these findings for human disease.

Dr Caroline Savage (University of Birmingham, UK) discussed the critical role of neutrophils in inflammatory renal disease with a special focus on antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis. She described new insights into the mechanisms by which cytokine-primed neutrophils are activated by autoantibodies, the subsequent neutrophil–endothelial cell interaction, neutrophil degranulation, and cytokine production (including IL-17), ultimately leading to endothelial and tissue damage.[19]

Dr Neil S. Sheerin (University of Newcastle, UK) reviewed the current understanding of how complement activation can mediate kidney injury and highlighted new areas in which complement components may have important regulatory roles. He reported that complement activation can directly injure tubular epithelial cells, induce synthesis of proinflammatory and profibrotic cytokines, and thereby lead to interstitial fibrosis and tubular atrophy.[20] Furthermore, he provided evidence that a fully functional complement system is essential for the alloimmune response after renal transplantation, which has important implications for inhibitor treatment.[21] Finally, he discussed the gaps in our knowledge and the challenges we face in developing complement therapeutics for use in the clinic.

Dr Gabriela E. Garcia (University of Denver, USA) discussed the role of A2a adenosine receptors as modulators of inflammation. Genetic and pharmacological evidence support a significant, nonredundant role for both adenosine and A_{2A} adenosine receptors ($A_{2A}R$) in protecting tissue from acute inflammatory damage. $A_{2A}R$ is expressed in several inflammatory cells including T regulatory cells. In experimental anti-glomerular basement membrane glomerulonephritis, $A_{2A}R$ is expressed in macrophages (Mϕ) from nephritic glomeruli and its activation reduces the degree of kidney injury in both the acute inflammatory phase and the chronic progressive phase of glomerulonephritis.[22] The pharmacological activation of $A_{2A}R$ reduces inflammation and ischemia–reperfusion injury in the liver, spinal cord, heart, lung, and kidney. It is considered one of the most potent endogenous anti-inflammatory mechanisms. Therefore, $A_{2A}R$ ligands, despite some remaining challenges, represent a therapeutic strategy for several inflammatory diseases.

ADAPTIVE IMMUNE RESPONSE: T-CELL SUBTYPES AND CHEMOKINES

$CD4^+$ effector T cells are important regulators of the immune response in autoimmunity and infection. They have originally been divided in two subsets (Th1 and Th2) according to the cytokine expression profile.[23] This dichotomy has been challenged in the recent years by discovery of $CD4^+$ FoxP3 (forkhead box P3)-expressing regulatory T cells (Tregs) and IL-17-producing Th17 cells.[24] Whereas Treg cells have their function in preventing excessive immune responses in inflammatory diseases, Th17 cells have been linked to the pathogenesis of autoimmune conditions including autoimmune kidney disease.[25] Therefore, two sessions of the ISN Forefronts meeting were dedicated to the advances in the field of T-cell immunology with a special focus on the role of chemokines and their receptors in $CD4^+$ T-cell trafficking.

Dr Ari Waisman (University of Mainz, Germany) provided an overview of the development of the Th17 field in the past years. The implication of Th17 cells in autoimmunity commenced with the discovery that IL-23 is essential for development of experimental multiple sclerosis and rheumatoid arthritis. The subsequent finding that IL-23 induces differentiation of Th17 cells gave rise to the notion that not Th1, but Th17, immune response mediates autoimmunity. IL-17 secretion was considered to be the main driving force in the pathogenesis of Th17-dependent autoimmunity. Dr Waisman's group generated mice in which T cells overexpress IL-17, and found that this did not accelerate pathogenesis of experimental multiple sclerosis. Conversely, mice lacking IL-17 production were fully susceptible to this experimental model. These findings challenge the view that IL-17 is the

central pathogenic mechanism for autoimmune disease in the central nervous system.[26] The true effector molecule(s) produced by Th17 remains to be identified.

Dr Richard Kitching (Monash University, Melbourne, Australia) discussed the potential role of Th17 cells in renal inflammation. In line with findings from experimental models of nonrenal autoimmunity, recent studies could demonstrate that the IL-23/Th17 axis contributes to immune-mediated kidney damage.[27–31] The Kitching group recently demonstrated in a cell transfer system that both Th1 and Th17 cells were capable of inducing glomerular injury.[30] In experimental anti-MPO-induced glomerulonephritis, IL-17 showed at least two effects: it caused initial neutrophil recruitment and subsequently stimulated MPO-specific effector $CD4^+$ T cells to cause glomerular injury.[31] Also, in nephrotoxic nephritis, IL-23-dependent Th17 cells and their mediator IL-17 were pathogenic, by mechanisms involving IL-17-induced production of chemokines that can recruit monocytes into the kidney.[27] These findings identify Th17 cells as new players in glomerular disease with an immune effector signature distinct of those from Th1 cells.

Dr Kathrin Eller (University of Innsbruck, Austria) summarized the recent progress in mouse models employing genetic or antibody-mediated ablation of Treg cells, as well as their adoptive transfer, that demonstrated the central role of these cells in glomerulonephritis. In nephrotoxic nephritis, Treg cells exerted suppressive effects in secondary lymphatic organs, where they limited the disease by downregulating effector T-cell activation.[32] The chemokine receptor CCR7 was crucial in guiding the Tregs to lymph node areas where antigen presentation takes place.[33] Later, it was shown that Treg cells also infiltrated the inflamed kidney tissue and suppressed the intrarenal immune effector phase, at that stage of the disease dependent on migration guided by the chemokine receptor CCR6.[34]

Dr Ulf Panzer (University of Hamburg, Germany) summarized the recent advances in the field of chemokine research and their relevance for T cell-mediated glomerulonephritis. In a recent study, his group demonstrated that not only immunosuppressive Treg cells, but also pathogenic Th17 cells use the chemokine receptor CCR6 for kidney-directed trafficking.[34] Furthermore, he described the unpublished observation that Th17 and Th1 cells sequentially infiltrate the kidney during a nephritogenic immune response, as a consequence of distinct chemokine receptor expression pattern. However, the functional importance of this finding has yet to be fully elucidated.

Dr Reinhold Förster (University of Hannover, Germany) discussed the role of homeostatic chemokines in the functional organization of the immune system. He provided insight into mechanisms that induce imprinting of certain homing properties to T cells and summarized the current knowledge of how tissue tropism in gut-homing T cells develops. Interestingly, stromal cells in the mesenteric lymph nodes were recently identified as important inductors of T-cell gut tropism *in vivo*.[35] Whether specialized T cells with kidney-homing properties exist is unknown and awaits further study.

Dr Marcus Thelen (Institute for Research in Biomedicine, Bellinzona, Switzerland) highlighted the important function of chemokine decoy receptors in balancing the immune response. Beside the extensively investigated scavenger receptors D6 and DARC (Duffy antigen receptor for chemokines) that contribute to resolution of inflammatory processes by sequestering a large number of inflammatory chemokines, recently, another nonsignaling receptor for the chemokine CXCL12 (chemokine (C-X-C motif) ligand 12) was discovered and termed CXCR7. Dr Thelen provided details on his recent results about CXCR7 and demonstrated that CXCR7 works as a specific and effective scavenger for CXCL12, suggesting a critical function in modulating the activation of the ubiquitously expressed CXCL12 receptor CXCR4.[36]

ADAPTIVE IMMUNE RESPONSE: B CELLS

Dr Anja Hauser (University of Berlin, Germany) highlighted the complex anatomical structure and spatiotemporal interactions of leukocytes in germinal centers that are the cradle of memory B and plasma cells. She introduced the utility of multiphoton microscopy to visualize B-cell migration in germinal centers *in vivo*. Her time-lapse movies revealed the germinal center to be a highly dynamic structure and demonstrated that functionally different B-cell subsets display individual types of motion.[37] Her presentation once more highlighted the need to consider the kinetics of immune responses.

Dr Oliver M. Steinmetz (University of Hamburg, Germany) introduced a new classification of renal B-cell infiltrates in human glomerulonephritis. B cells are regularly present in experimental and human inflammatory kidney disease.[38,39] These infiltrates have so far been regarded as a single entity, although in fact being quite heterogeneous. Microanatomical analysis of renal B cells in patients with lupus- and ANCA-associated nephritis revealed four increasingly organized levels ranging from a scattered distribution to highly compartmentalized B-cell clusters resembling secondary lymphoid tissue with germinal centers and follicular DC networks.[40] This new classification of B-cell infiltrates might help to clarify contradictory findings from the past about their clinical significance.

Dr Michael Mengel (University of Edmonton, Canada) critically reviewed the multiple and complex roles of B cells in renal transplant rejection. He presented studies that correlated expression of B cell-associated transcripts and immunoglobulin transcripts with histopathology and function of renal allografts. Although the expression of B cell-associated transcripts and immunoglobulin transcripts correlated with renal function, this relationship was because of differences in early vs late biopsies and neither B cell-associated transcripts nor immunoglobulin transcripts were related to allograft function after correcting for time.[41] Furthermore, his microarray analyses revealed that areas with

interstitial fibrosis and tubular atrophy are associated with a distinctive pattern of inflammatory molecules, including B cell/immunoglobulin- and mast cell-associated genes, which correlated with poor outcomes.[42] Dr Mengel also presented functional studies of renal transplantation in mice, showing that the absence of B cells in the recipient has no influence on early rejection of allografts, but in contrast on long-term maintenance of the inflammatory response. Thus, onset of chronic injury is dependent on the presence of B cells.

Dr Reinhard E. Voll (University of Erlangen, Germany) discussed the role of plasma cell depletion as a novel therapeutic strategy for systemic lupus erythematosus. His group demonstrated that treatment with the proteasome inhibitor bortezomib depleted plasma cells in NZB/W F1 (New Zealand Black/White F1) lupus-prone mice including the pathogenic anti-double-stranded DNA-producing subset. In bortezomib-treated mice, development of lupus nephritis was prevented and survival was dramatically prolonged. Even when bortezomib treatment was started at later time points with well-established lupus nephritis, proteinuria resolved and treated mice survived significantly longer.[43] Hence, as Dr Voll explained, proteasome inhibition may represent a novel therapeutic strategy for autoantibody-mediated diseases including systemic lupus.

Dr Peter Heeringa (University of Groningen, The Netherlands) provided an overview about the role of antibodies in ANCA-associated forms of rapidly progressive crescentic glomerulonephritis. ANCAs comprise a group of autoantibodies directed against lysosomal enzymes contained in neutrophils and monocytes that are associated with small-vessel vasculitides. Based on clinical and *in vitro* experimental evidence, a pathogenic role for these autoantibodies has long been suspected in ANCA-associated glomerulonephritis.[44] However, to study the complex interplay between ANCAs, neutrophils, and the local environment, animal models are required. Here, Dr Heeringa presented the animal models developed for ANCA glomerulonephritis and discussed how these models have been applied to study the autoantibody-mediated effector mechanisms. Finally, Dr Heeringa proposed directions for future research regarding unresolved issues relevant for the pathogenesis of ANCA glomerulonephritis.[45]

IMPLICATIONS FOR HUMAN INFLAMMATORY RENAL DISEASE

Dr William G. Couser (University of Seattle, USA) summarized the state-of-the-art knowledge of the development of membranous glomerulonephritis, data that were primarily obtained from experiments in the animal model of passive Heymann nephritis.[46,47] These studies lay ground to the landmark observations recently made in human membranous nephropathy.[48] Salant's group found that 70% of patients with primary membranous nephropathy have circulating autoantibodies against the M-type phospholipase A_2 receptor. In the kidney, this receptor is exclusively expressed on glomerular podocytes. By immunofluorescence it was shown that the autoantibodies, which primarily belong to the IgG4 subclass, bind to podocytes. Although not formally proven, the data suggest that the autoantibodies after binding to podocytes may bind and activate complement and initiate disease. These findings are of great clinical importance as they may eventually allow separating primary from secondary membranous nephropathy. Furthermore, serum autoantibody levels may help guide therapy.

Dr Renate Kain (University of Vienna, Austria) discussed the role of lysosomal membrane glycoprotein 2 (LAMP-2) in ANCA-associated vasculitis. The Vienna group recently discovered autoantibodies to human LAMP-2 as antigenic targets in patients with ANCA-associated pauci-immune focal necrotizing glomerulonephritis (FNGN).[49] Dr Kain provided evidence for their prevalence and pathogenetic role. Specifically, she showed that: (1) circulating anti-LAMP-2 antibodies can be detected in almost all patients presenting with ANCA-associated FNGN; (2) antibodies to LAMP-2 cause pauci-immune FNGN when injected into rats; and (3) a monoclonal anti-hLAMP-2 antibody induces apoptosis of human microvascular endothelium *in vitro*. Furthermore, peptide mapping identified two common human LAMP-2 epitopes in the patients' anti-LAMP-2 autoantibodies and one (P_{41-49}) was 100% homologous to the bacterial adhesin FimH. Binding studies showed that the patients' anti-P_{41-49} autoantibodies crossreact with FimH. As infections with fimbriated pathogens can often be observed before the onset of FNGN, the exposure to FimH may provide a biomimicry that allows the development of an autoimmune to LAMP-2 that may mediate the development of pauci-immune FNGN.[49]

Richard J. Johnson (Denver, CO, USA) presented evidence that minimal change disease might be mediated by the expression of the DC-associated antigen CD80 (also known as B7.1). Studies by Reiser *et al.*[50] had previously shown that TLR ligands, such as lipopolysaccharide, can induce the expression of CD80 in podocytes in mice, resulting in actin rearrangement and proteinuria. CD80 is normally expressed by DCs and has an important role in T-cell activation. For a long time, minimal change disease had been thought to be a T-cell disorder, and some evidence from animal models suggested that it may involve podocyte expression of CD80.[51] Consistent with these experimental studies, Garin *et al.*[52] were recently able to show that corticosteroid-sensitive minimal change disease is associated with both glomerular podocyte expression of CD80 and increased urinary excretion of CD80.Unpublished experimental studies suggest that CD80 might be induced in podocytes both *in vitro* and *in vivo* by various TLR ligands to TLR3 and TLR4. Further studies to identify the factors both inducing and causing the persistent expression of CD80 in the podocytes of patients with minimal change disease are ongoing.

CONCLUSION

ISN Forefronts Symposia have been designed to advance scientific nephrology and familiarize nephrologists with emerging fields in basic research that have a fundamental

impact on the understanding, diagnosis, and treatment of renal diseases. In perfect line with these aims, the 2010 ISN Forefronts Symposia 'Induction and Resolution of Renal Inflammation' on the secluded island of Sylt allowed the 100 participants to review current knowledge, to discuss latest developments and new concepts in the field of inflammation, and to provide a setting for an in-depth look into exciting ideas that are changing the way we look at renal care.

DISCLOSURE

All the authors declared no competing interests.

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